



PK-CM Sub-study

Study AC-060A202: CONTROL
Patricia Sidharta



PK-CM sub-study

- Objectives
 - To evaluate the pharmacokinetics (PK) in this patient population
 - To confirm the safety profile of ACT-129968 (cardiac monitoring)
 - Comparison of fasted and fed state PK under steady-state conditions in patients
 - ➔ To guide dosing in Phase 3 and in children
- Performed at select sites
 - 120 patients
 - must sign Addendum 1 ICF (voluntary)

Study assessments PK-CM sub-study

Only performed at selected sites

PERIODS	Name	SCREENING	TREATMENT						RUN-OUT	FOLLOW-UP
	Duration	2 weeks	12 weeks						2 weeks	2 weeks
VISITS	Name	Visit 1 Screening	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 End-of-Treatment	Visit 8 End-of-Study	Safety follow-up ⁶
	Time	Week -2 (-4/+2 days)	Day 1	Week 1 (-1/+3 Days)	Week 2 (-1/+3 Days)	Week 4 (-1/+3 Days)	Week 8 (±3 Days)	Week 12 (±3 Days)	Week 14 (-1/+3 Days)	EOT + 30 Days (±1 Day)
Informed consent – Addendum 1 ¹		X								
**Blood sampling fasted ²					X					
**Blood sampling fed ³						X				
**Holter cardiac monitoring ⁴		X			X	X				
**ECG (12-lead) versus time profiles ⁵					X	X				

1. The PK-CM will be conducted at selected centers (optional and voluntary). Patient must have signed Addendum 1 to the ICF.
2. Blood sampling over 12 hours without breakfast to determine the pharmacokinetic profile of ACT-129968.
3. Blood sampling over 12 hours after a high-fat, high-calorie breakfast to determine the pharmacokinetic profile of ACT-129968.
4. 24-hour 12-lead Holter cardiac monitoring at Screening and 12-hour Holter cardiac monitoring at Visit 4 and Visit 5. Instructions provided at Visit 1.
5. ECG (12-lead) will be extracted from the 12-lead Holter monitoring at the pre-specified PK blood-drawing time points.
6. The SAE follow-up visit will be performed by phone 30 days after EOT.

* Recorded in CRF.

** Electronically transferred to sponsor.

CRF = case report form; ECG = electrocardiogram; EOT = end-of-treatment; ICF = informed consent form; PK = pharmacokinetic(s); PK-CM = pharmacokinetic cardiac monitoring; SAE = serious adverse event.

PK-CM sub-study: PK profiles at Visit 4 and 5

PK sampling at specified time points over a 12-hour period after drug administration in the clinic

– **Visit 4: drug administration in fasted state**

- Patients should come fasted to the clinic
- Patients that are not fasted should be rescheduled within the Visit window
- Trough PK sample must be taken before the morning study drug dose
- Patient must not eat in the 4-hour time period after morning dose

– **Visit 5: drug administration in fed state**

- Patients should come fasted to the clinic
- Trough PK sample must be taken before breakfast

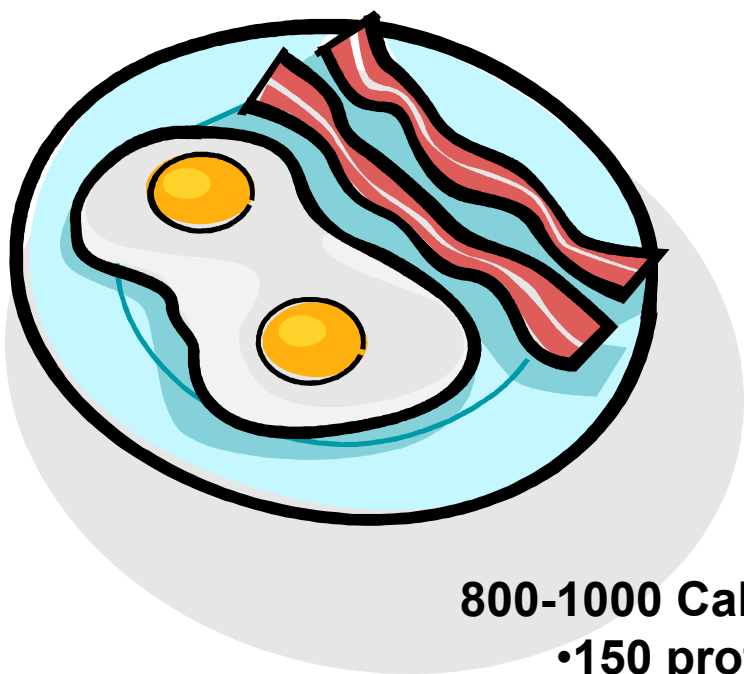
PK-CM sub-study: Meal at Visit 5

Visit 5: Meal

- A high-fat, high-calorie breakfast is given to patient in clinic
 - Composition of meal must follow FDA guidance
 - Patients should eat the complete meal within 30 minutes
 - A source record of meal completion (Meal Completion Form) should be filled out at Visit 5
 - Patients not eating entire meal will be Protocol Violators
 - Drug should be administered 30 minutes after start of meal
 - Each site should record composition of meal that will be provided to all patients in source data worksheet (Composition of Meal at Visit 5 Form)

PK-CM sub-study: Meal at Visit 5 (cont)

High Fat High Calorie Breakfast Example:



800-1000 Calories
•150 protein
•250 carbohydrate
•500-600 fat

PK-CM sub-study: Meal at Visit 5 (cont)

Menu Examples

- **McDonalds**
 - 1 Sausage McMuffin
 - 1 Sausage McMuffin with egg
 - Hashbrowns (56g) or 240 mL Milk (3.5%)
- **Meat**
 - 2 eggs (10g butter)
 - 2 strips bacon
 - Hash browns (120 g)
 - 2 slices of toast (10 g butter)
 - (or 3 slices of toast, no hashbrowns)
 - 240 mL milk (3.5%)
- **Vegetarian 1**
 - 1 egg (10 g butter)
 - 2 slices of toast (15 g butter)
 - 50 g camembert
 - Hash browns (120 g)
 - 200 ml milk (3.5%)
- **Vegetarian 2 (No Pork)**
 - 2 eggs (15 g butter)
 - 3 slices of toast (15 g butter)
 - 200 mL milk (3.5%)
 - 30 g Cashew nuts

PK-CM Sub-study: Composition of Meal at Visit 5 Form



ACTELION Creative Science for Advanced Medicine		Composition of Meal at Visit 5	Version 2
Compound: ACT-129968	Indication: Asthma	Protocol #: AC-060A202 / CONTROL	
Site identification			
<div style="border-bottom: 1px solid black; width: 100px; margin: 0 auto;"></div> site number		<div style="border-bottom: 1px solid black; width: 200px; margin: 0 auto;"></div> name of Principal Investigator	

This document should be completed only by sites who are participating in the PK-CM sub-study. The composition of meal provided at Visit 5 must follow FDA guidance (i.e., High-Fat, High-Calorie Breakfast must contain 150 calories protein, 250 calories carbohydrate and 500-600 calories fat).



Please check the box/es next to the meal/s that are used at the site.

- | | |
|---|---|
| <input type="checkbox"/> <u>McDonalds:</u>
- 1 sausage McMuffin
- 1 sausage McMuffin with egg
- Hashbrowns (56g) or 240 ml milk (3.5%) | <input type="checkbox"/> <u>Vegetarian 1:</u>
- 2 eggs (15g butter)
- 3 slices of toast (15g butter)
- 200 ml milk (3.5%)
- 30g Cashew nuts |
| <input type="checkbox"/> <u>Meat:</u>
- 2 eggs (10g butter)
- 2 strips bacon
- Hashbrowns (120g)
- 2 slices of toast (10g butter) or 3 slices of toast and no Hashbrowns
- 240 ml milk (3.5%) | <input type="checkbox"/> <u>Vegetarian 2:</u>
- 1 egg (10g butter)
- 2 slices of toast (15g butter)
- 50g Camembert cheese
- Hashbrowns (120g)
- 200 ml milk (3.5%) |

PK-CM Sub-study:

Composition of Meal at Visit 5 Form (cont)

- Other meal compositions are allowed
- Please contact your Monitor for further details

 ACTELION <small>Creative Science for Advanced Medicine</small>		Confirmation of Site-specific Meal		Version 1
Compound: ACT-129968		Indication: Asthma		Protocol #: AC-060A202 / CONTROL

Site identification	
<div style="border-bottom: 1px solid black; width: 100px; margin: 0 auto;"></div> site number	<div style="border-bottom: 1px solid black; width: 200px; margin: 0 auto;"></div> name of Principal Investigator

Date: DDMMYYYY


The meal below was confirmed by Actelion.



Site-specific meal:

-
-
-
-
-
-
-
-

PK-CM Sub-study: Visit 5 Meal Completion Form

 ACTELION <small>Creative Science for Advanced Medicine</small>	Visit 5- Meal Completion		Version 1
	Compound: ACT-129968	Indication: Asthma	Protocol #: AC-060A202 / CONTROL
Patient identification			
<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;"> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> </div> <div style="text-align: center;"> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> <div style="border-bottom: 1px solid black; width: 100px; height: 15px;"></div> </div> <div style="display: flex; justify-content: space-around;"> subject number site number </div> </div>			

This document should be completed only for patients who are participating in the PK-CM sub-study. The Meal Completion form must be completed at Visit 5, following the intake of High-Fat, High-Calorie Breakfast.

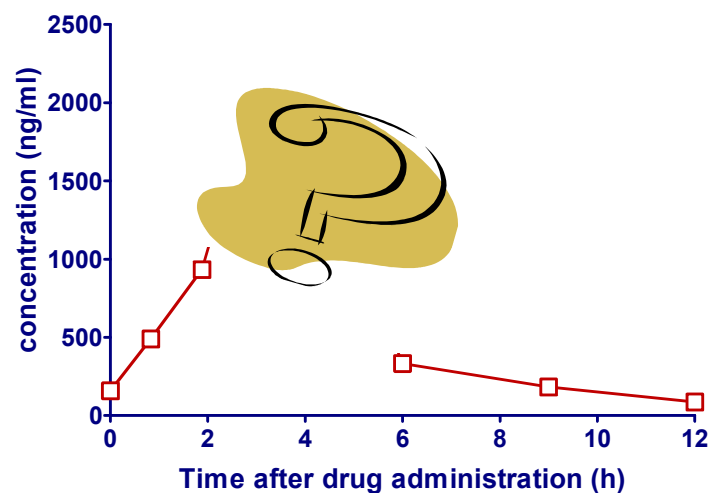
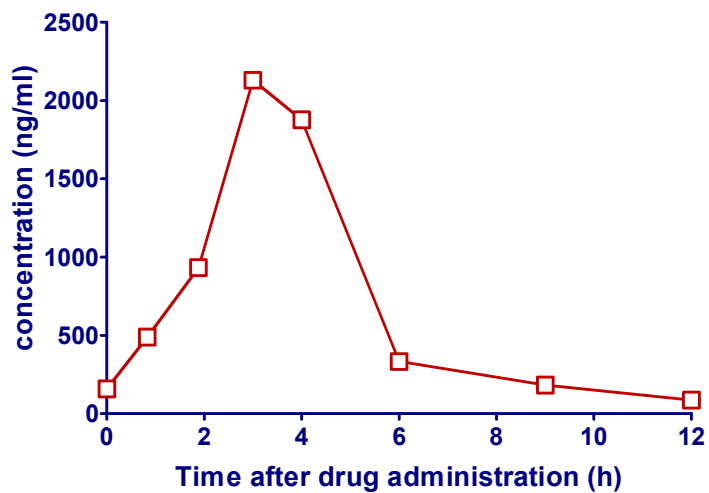
Did patient eat the High-Fat, High-Calorie Breakfast?	Yes	No
	<input type="checkbox"/>	<input type="checkbox"/>

- Meal should be eaten within 30 minutes.
- Study drug should be administered 30 minutes after start of meal.
- If meal is not finished within 30 minutes, perform dosing at 30 minutes and let the patient continue eating.

Name of investigator			
Date		Signature	

PK-CM sub-study: Recording of data

Exact recording of drug administration time and PK sampling time is key!



Study drug administration and PK sampling - Visit 3-7 and Unscheduled Visits

Study Drug Admin – Last 24hrs:

- Enter the date of the last morning dose and the date of the last evening.
- Enter the number of capsules taken by the subject at each dose

Study Drug Administration – Last 24 hours		SDV
Date of administration	Number of capsules administered	CHK
Last morning dose 09 APR 11 [dd mmm yy]	4	<input type="checkbox"/>
Last evening dose 09 APR 11 [dd mmm yy]	3	<input type="checkbox"/>
		SDV

PK Sampling:

- This is the trough pre-morning dose PK sampling that should be collected from ALL patients

- Enter the date and time of sampling

PK Sampling		SDV
Date of sampling	Time	CHK
10 APR 11 [dd mmm yy]	0958 [hh mm]	<input type="checkbox"/>
		SDV

PK-CM Sub-study – Visit 4 & 5

- Only complete this page if patient is participating in the PK-CM sub-study.
- Enter the starting time
 - Complete meal should be consumed within the 30 min before drug administration
- Enter the date at least for 0.5h sampling. If all samples are taken on the same day, leave the subsequent date fields empty.
- Enter the “actual” time and not the scheduled time.

Actelion Pharmaceuticals Ltd
AC-060A202

Page : 11

**Visit 5 / Week 4
PK-CM Study**

Tick if page is empty ☐

High-Eat, High-Calorie Breakfast
 Date 03 NOV 10 Time 09:09
[dd mmm yy] [hh mm]

Study Drug Administration – Morning
 Date of administration 03 NOV 10 Time 09:39
[dd mmm yy] [hh mm]
 Number of capsules administered (ACT-129968/Placebo) 4

Blood Sampling for PK-CM Sub-study (fed)

Study time (relative to last study drug administration)	Date of sampling [dd mmm yy]	Actual time [hh mm]
0.5 h	03 NOV 10	10:00
1 h	03 NOV 10	10:35
1.5 h	03 NOV 10	11:03
2 h	03 NOV 10	11:30
3 h	03 NOV 10	12:40
4 h	03 NOV 10	13:39
5 h	03 NOV 10	14:35
6 h	03 NOV 10	15:30
8 h	03 NOV 10	18:39
12 h	03 NOV 10	21:25

For sponsor use only
☐ CHK
☐ SDV
☐ CHK
☐ SDV
☐ CHK
☐ SDV

PK-CM sub-study: Cardiac monitoring

- ECG Holter monitoring
 - 24 hr Holter at V1
 - 12 hr Holter at V4 and V5
 - ECGs extracted from Holter at specific time points to explore ECG effects vs concentration.

PK-CM sub-study: Key messages

- Visit 4 (fasted) and 5 (fed) both must be completed in order to compare fasted and fed state in a patient.
- Should eat meal within 30 minutes and dose immediately thereafter (if meal not finished within 30 minutes, perform dosing at 30 minutes and continue eating)
- Composition of meal must follow FDA guidance
- Must eat entire meal (will be recorded on a specific source data form)
- Proper recording of drug administration and PK sampling time is key
- Only by accurately following the protocol can concentration-time and effect/safety-concentration relationships, and effect of food be investigated



PK sample processing

ACM Global - Central Laboratory

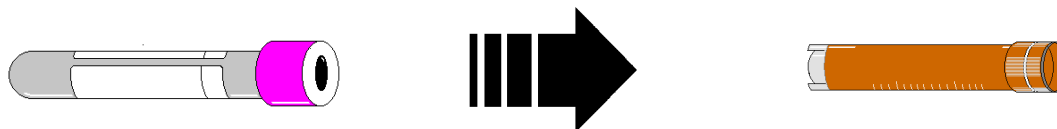


ACM Services for AC-060A202 PK samples

- Specimen Storage
- Provision of Laboratory kits
- Sample Collection & processing instructions
- Sample shipping logistics
- Data Resolution

Sample Processing

2ml EDTA Purple Top Tube – PK, Visits 3, 4, 5, 6, 7 and Unscheduled (Plus Visits 4 and 5 for PK-CM Sub-Study Patients)



- 1 – Draw the 2ml EDTA tube
- 2 - Gently invert the tube for 10-15 seconds to ensure proper mixing of anticoagulant and blood
- 3 – Place the EDTA tube on ice and perform sample processing within 30 minutes
- 4 - Centrifuge the tube **at 2000g for 10 minutes at 4°C ***
- 5 - Remove the tube from the centrifuge after spinning and pipette all the plasma (top clear layer) into **1 x 2mL amber cryovial** provided at each draw
- 6 – **FREEZE IMMEDIATELY** at –20°C until shipping

No Refrigerated Centrifuge?

- Cool the element in the fridge, or fill the bucket with ice
- After blood draw and sample inversion, cool sample on ice
- Within 30 minutes, centrifuge sample at 2000g for 10 minutes in a centrifuge with pre-cooled elements.



Holter monitoring

eResearchTechnology, Inc. (ERT)



ERT services

- ERT to provide ELI 150 ECG machine (12-lead ECG) and H12+ Holter device (Cardiac monitoring)
- Please refer to ECG presentation for:
 - My Study Portal
 - Actions of equipment arrival
 - Customer Care
 - Study setup
 - 12-lead ECG recording
 - Query process
 - Return of ECG material

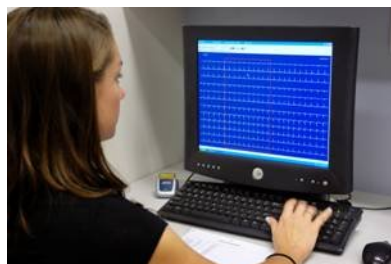


The Holter Extraction Collection Process

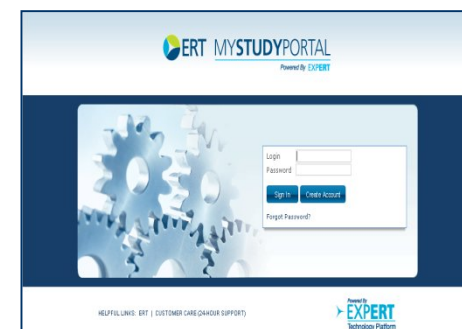
Holter Recording
Captured at Site



Mailed



Analyzed at
ERT



ECG Results
reported to site
via My Study
Portal



The Holter Arrhythmia Collection Process



Holter Recording
Captured at Site



Analyzed at
ERT



Results reported
to site via fax

**Mailed via
courier to ERT**



Mortara H12+



**Complete
Transmittal
Form**



**Record
Holter**



**Mail Flashcard &
Transmittal Form
to ERT**

Holter Visit Schedule

Actual Visit name
VISIT 1 (SCREENING)
VISIT 4 (WEEK 2)
VISIT 5 (WEEK 4)

Mortara H12+

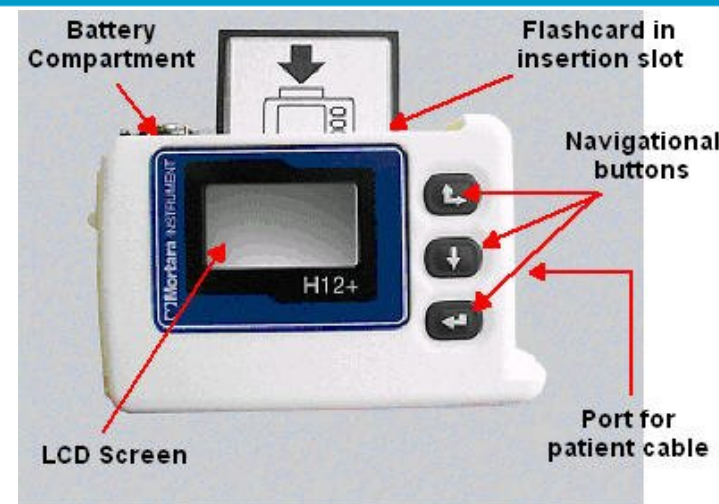


- Digital Holter recorder
- 12 lead data recording over 24 hour period
- Data stored on compact flashcard
- Single AA Battery Power
- Ability to test lead quality and lead amplitude

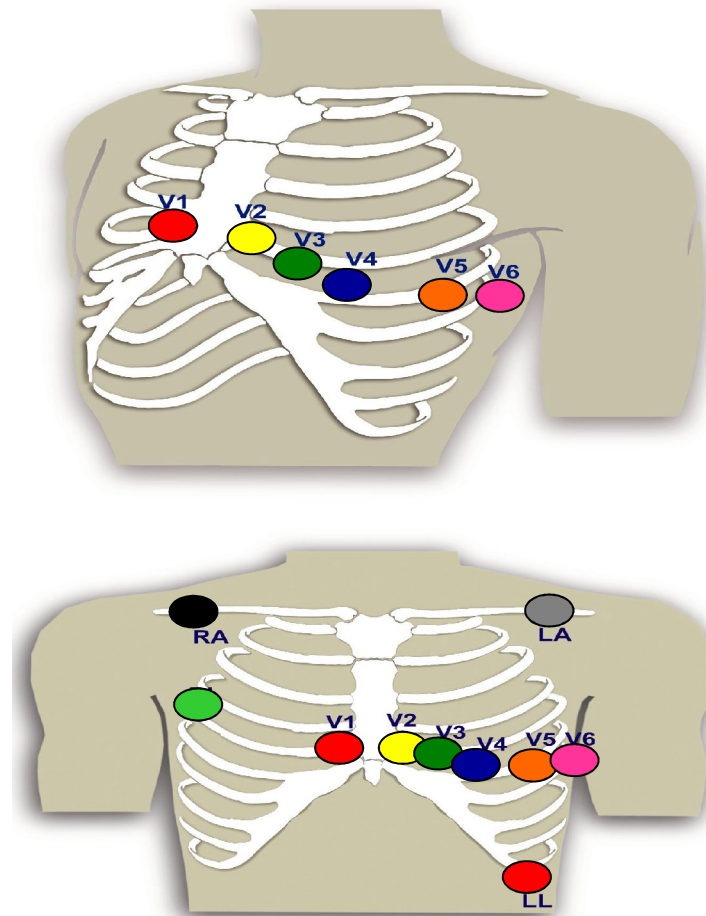


Holter Processing Overview

- Complete transmittal form
- Record serial number of Holter device and flashcard
- Insert new battery for each 24 hour recording
- Check lead quality and lead amplitude
- Begin recording
- The recorder will automatically stop recording after 24 hours
- Remove battery and flashcard
- Ship transmittal form and flashcard

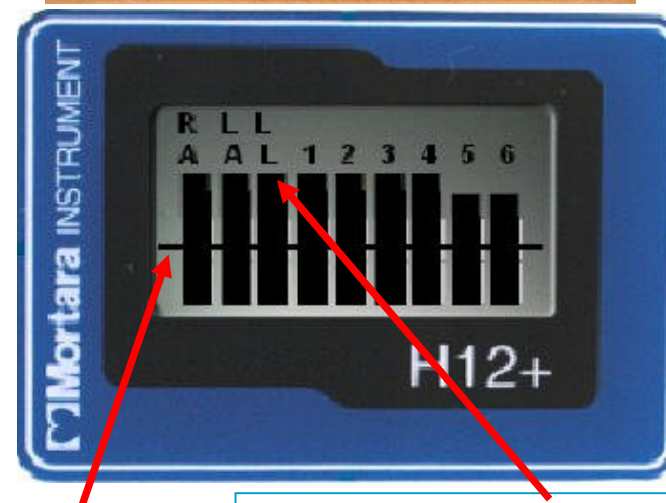


Standard Holter Electrode Placement



Quality Assurance Lead Check

- Using the up and down arrow keys, scroll to the menu option 'LEAD CHECK'
- A full-bar graph means high quality signal and good electrode contact.
- For good quality recordings, the bars must reach or exceed the horizontal line on the display.



Horizontal line

Good impedance



Quality Assurance Display ECG

- Using the up and down arrow keys, scroll to the menu option “DISPLAY ECG”
- Scroll through the different leads to verify amplitude and signal strength.



Recording Holter

- Using up and down arrows, scroll to menu option “RECORD”
- Press the “ENTER” key to begin recording.
- During normal operation the current time is displayed and the message “RECORDING” is displayed



Transmittal Form

H12+ Data Transmittal Form		Transmittal #:	
Sponsor: Actelion Pharmaceuticals Ltd Protocol: AC-060A202 Version: 1			
<small>Complete the information below for each Flashcard being sent to ERT (refer to the ERT Quick Guide for detailed instructions)</small> <small>Synchronize clinic clock and H12+ clock prior to each recording</small>			
Retain bottom copy for your records. Send top copies, with flashcard, to ERT via UPS at the following address: ERT 1818 Market Street Suite 1000 Philadelphia, PA 19103			
Principal Investigator:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Site ID: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Site Tech Initials: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Recorder Serial Number (S/N):	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	FC Serial #:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Patient Number:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
Gender:	<input type="checkbox"/> MALE <input type="checkbox"/> FEMALE	Age (at screening visit)	<input type="text"/> <input type="text"/>
CHECK VISIT: <input type="checkbox"/> VISIT 1 (SCREENING) <input type="checkbox"/> VISIT 4 (WEEK 2) <input type="checkbox"/> VISIT 5 (WEEK 4) <input type="checkbox"/> UNSCHEDULED			
Recording Start Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
Recording Start Time:	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/> (time when user pushes the 'RECORD' button)		
Dosing Time:	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/> (24 hour clock)	ERT to query if dosing time is prior to recording start time	
<<ERT USE ONLY: SITE DOES NOT WRITE BELOW THIS LINE>>			
ERT Account Number:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Office: Peterborough	
Workstation Number:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Slot #:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
RECEIPT DATE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	DC ID:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
DC INITIALS:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	PROCESSED DATE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
CSS ID:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	CSS INITIALS:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
EXTRACTIONS EXPORTED DATE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	CSS ID:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
CSS INITIALS:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	STATISTICS EXPORTED DATE	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
CSS ID:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	CSS INITIALS:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Alert Form (if applicable) <input type="checkbox"/> Failure Notification			
PLACE SCAN LABEL HERE			

- Multiple page NCR Form
- Complete demography and visit information
- Keep bottom copy for site records
- Submit to ERT with flash card
- The dosing time is very important in order to correctly extract ECGs from Holter



Shipping the Flash Card to ERT

- Place the completed Transmittal Form and flash card in a padded envelope
- Place the padded envelope in a courier envelope
- Attach a completed courier airway bill and send
- Please refer to the Investigator Manual for additional instructions

Holter Analysis Report

ERT
Getting It Done. Right.

**FACSIMILE REPORT
Holter Feedback Form**

ACTELION
AC-060A202

INVESTIGATOR: _____
FAX TO SITE: _____
E-mail to: Clare Winfield (cwinfield@ert.com); Andy Gilbert (agilbert@ert.com)

Patient Number: _____
Transmittal Number: ACCT # 746159

Visit (circle one): Visit 1 Visit 4 Visit 5

There were Technical Problems with Holter: ☐ Yes, see comments ☐ No

Comment: _____

QC Specialist: _____ Date: _____

CARDIOLOGIST EVALUATION (ALERTS BOLDED)

☐ **NORMAL**
☐ **ABNORMAL**

☐ Frequent VPCs (☐ _____ in _____ hours) ☐ (> 30 VPCs in one hour)

☐ **Nonsustained Ventricular Tachycardia** (_____ episodes)

☐ **Sustained Ventricular Tachycardia**

☐ **Salvo de Pointes**

☐ **Ventricular Fibrillation or Ventricular Flutter**

☐ Frequent short episodes of Nonsustained Supraventricular Tachycardia

☐ **Atrial Fibrillation**

☐ **Atrial Flutter**

☐ Mobitz I (Wenckebach) 2nd Degree AV Block

☐ **2:1 AV Block**

☐ **High Grade AV Block**

☐ **Mobitz II 2nd Degree AV Block**

☐ **Complete Heart Block**

☐ **Pause > 3.0 seconds** (longest pause _____ seconds)

☐ **Average Heart Rate < 40 for any one hour**

☐ Marked Sinus Bradycardia

☐ Intermittent Ectopic Atrial Rhythm

☐ Intermittent Junctional Rhythm

☐ Other _____

☐ **UNABLE TO EVALUATE**
☐ No data obtained

COMMENTS: _____

Interpreted By: Robert Kleiman, M.D. Dai Rowlands, M.D. Svetlana Nikitina, M.D. Date _____

ERT
Getting It Done. Right.

eResearch Technology
30 South 17th Street
Philadelphia, PA 19103-4001
Option 1 (US and Canada) / +1-800-555-2020, Option 1 (International)

Demography Information

Initials: MLA Holter Trans No: 1688
Subject Number: 12345 eRT #: 999999 Sex: Female Date Recorded: 1/2/2007 16:08:24
Holter Visit: DAY 1 Scan Date: 1/4/2007
Protocol: IG_HSCRIE_3.00 Date Of Birth: 1/1/1979
eRT Evaluation: Normal
Recorder: H12.Cont.3.14 Recorder No: 123456789012 Screen No: 002 Site No: 600c

Scan Criteria

SVPB Prematurity: 20 % Pause: 2000 msec
ST Segment Elevation: 200 µV Long RR/Pause: All Beats
ST Segment Depression: 100 µV Pause Excluded From HR: No

Summary Statistics

Rate Statistics: Min Rate: 60 at 16:08:27 Total QRS: 86408
Max Rate: 60 at 16:08:27 Monitoring Period: 24 hr, 0 min
Mean Rate: 60

Supraventricular Ectopy: AFib (Time%)/peak avg. rate: 0 / 0 BPM
Singles: 0
Couplets: 0
Runs: 0

Ventricular Ectopy: Singles: 0
Couplets: 0
Runs: 0

Total: 0 R on T: 0
Total: 0

Pauses: Longest RR: 1.00 sec at 16:08:23 # RRs > 2.0 sec: 0

Comment: _____

eRT Account: 999999

- Preliminary report - sent within 72hours of receipt at ERT via fax to site
- Full report – hard copy sent in 7-10 days via courier





Thank You

